Abstract #15740

BILE ACID PROFILES PREDICT HEPATIC DECOMPENSATION IN PRIMARY SCLEROSING CHOLANGITIS.

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Abstract Text:

Background:

Patients with primary sclerosing cholangitis (PSC) often demonstrate increased plasma bile acid (BA) concentrations due to ongoing cholestasis. However, the relationship between composition of the BA pool and future development of hepatic decompensation (HD) remains unclear. Here we aim to establish whether bile acid profiles are predictive of decompensating events, and thus, potentially useful in prognostic settings such as stratification into clinical trials.

Methods:

Plasma BA profiles and alkaline phosphatase (AP) levels of 425 PSC patients were measured using clinically-available assays. Cox proportional hazard models were run for each BA and AP level predicting time to HD (defined as ascites, variceal hemorrhage or encephalopathy) with resulting hazard ratios reflecting risk at the 75th percentile relative to the 25th percentile. Gradient boosting, a machine learning technique, was used to build multivariable models predicting development of HD. The Harrell's concordance statistic (C-statistic) was used to measure the discrimination ability of the various models and probability of HD was estimated using Kaplan Meier curves.

Results:

The median age at study recruitment was 49 (range 10-80) and 42% were female. 51 HD events were observed over 1377 person-years. The median total BA level was 15.3µmol/L (range 0.5-646.5). The median AP level, in relation to the upper limit of normal (ULN), was 1.4 (range 0.2-13.1). Total BA and 9 out of 20 individually measured BAs were significantly associated with HD (p<0.001), with hazard ratios ranging from 1.13 (Total BA) to 1.017 (Tauroursodeoxycholic acid "TUDCA") and C-statistics ranging from 0.83 (Taurochenodesoxycholic acid "TCDCA") to 0.57 (UDCA). TCDCA was the strongest single-BA predictor of HD, with a 6-fold increase in HD event rate in patients with TCDCA concentration >5µmol/L compared to those with TCDCA <5µmol/L (Figure 1). Using a gradient boosting model, the combination of AP and multiple BAs (TCDCA, TUDCA, TLCA, TCA, GDCA, total BA, LCA, CDCA) with age and gender had an impressive C-statistic of 0.95. Removal of AP did not have a significant effect (C-statistic = 0.94), demonstrating the ability of the BA profile to predict HD events. Notably, this BA-based model outperformed conventional prognosticators including AP > 1.5XULN (C-statistic = 0.64) and the recently reported PSC risk estimate tool (PREsTo) (C-statistic = 0.86).

Conclusion:

Using a machine learning approach, we demonstrate that BA profiles are independently capable of predicting future HD events in PSC patients. Future studies to validate the results and incorporate additional variables are needed. However, our study suggests that BA profiles have prognostic value and should be considered in disease management and as an exploratory endpoint in future clinical trials.

Figure 1: Event rates of hepatic decompensation stratified by the range of TCDCA concentration

TCDCA.gp4	N	Events	Time	Event rate	CI (rate)
[0,5]	365	29	1228	0.024	0.016 - 0.034
(5,10]	29	9	82	0.110	0.050 - 0.208
(10,100]	31	13	66	0.196	0.104 - 0.335